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Targeting Brain-Eating Amoebae Infections

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ABSTRACT: Brain infections due to *Acanthamoeba* spp., *Balamuthia mandrillaris*, and *Naegleria fowleri* often lead to death. Despite differences in the preferential sites of infection in the brain, the mode of delivery of drugs is often intravenous. Here, we discuss targeted therapeutic approach to affect parasite viability without affecting the host cells, with an eye to improve formulation of drugs and/or administration of drugs against brain-eating amoebae.

KEYWORDS: *Protist, free-living amoebae, brain infection, central nervous system, acanthamoeba, balamuthia, naegleria*

Among free-living amoebae, *Acanthamoeba* spp., *Balamuthia mandrillaris* and *Naegleria fowleri* are well-known to infect the brain.[1−3] The most distressing aspect is that the fatality rate has remained more than 95%, despite our advances in antimicrobial chemotherapy and supportive care. *N. fowleri* produces an acute, fulminating primary amoebic meningoencephalitis (PAM) that results in death within days. *N. fowleri* gains access via the nasal passage through contaminated water, travels along the olfactory neuroepithelium, passes through the cribriform plate to reach the brain, and leads to brain tissue destruction.[1−3] In contrast, *Acanthamoeba* and *B. mandrillaris* produce chronic granulomatous amoebic encephalitis (GAE). *Acanthamoeba* spp. and *B. mandrillaris* enter the host through skin ulcerations and lower respiratory tract, spread hematogenously, and cross the blood-brain barrier to infect the brain. Despite differences in the mode of infection, the mode of drug delivery for both infections remains intravenous application of a mixture of drugs (amphotericin B, sulfamethoxazole, trimethoprim, and rifampicin against *Acanthamoeba* spp.; flucytosine, fluconazole, azithromycin, pentamidine, sulfadiazine, azithromycin, and miltefosine against *B. mandrillaris*, and amphotericin B, fluconazole, rifampin, azithromycin, dexamethasone, and miltefosine against PAM);[4] however, the prognosis remains poor, albeit these drugs being highly effective *in vitro*. A complete understanding of the preferential site of infection[5] could lead to improved drug discovery/formulation and application of drugs (e.g., intranasal *versus* intravenous) to target this devastating infection. There are several challenges associated with the intravenous application of drugs, including the following: (i) high selectivity of the blood-brain barrier; (ii) when given intravenously, drugs target all tissues primarily due to systemic dissemination and diluting their effects needlessly and can affect their physiology before reaching the target site in the brain; (iii) drugs have to be given at high concentration to achieve minimum inhibitory concentration at the target site following intravenous injections, and/or drainage into the blood following CSF injections; (iv) chemical composition of drugs given intravenously must get through the brain microvessels to target the intracerebral *N. fowleri*; (v) poor pharmacodynamics and pharmacokinetics profiles of available drugs; (vi) patient's medical conditions; and (vii) patient's tolerance and *Acanthamoeba* susceptibility to amoebicidal agents. Hence, there is a need to develop a targeted therapeutic approach, or identify drugs that can affect parasite viability without affecting the host cells. While reviewing several cases reported between 1968 amd 2016, it is observed that the location of lesions for GAE is most common in the frontal, parietal, occipital, and temporal lobes, while lesions are most frequent in the frontal lobe for PAM. This is consistent with the fact that both *Acanthamoeba* and *B. mandrillaris* disseminate via the hematogenous route, likely through the middle cerebral artery, as these cortices are among the main regions for middle cerebral artery supply, resulting in their widespread distribution. Lesions due to *N. fowleri* are mostly found in the frontal lobe due to anatomical proximity of olfactory bulb to the frontal lobe, which is consistent with its entry via the nose. Thus, intranasal application of drugs could prove to be an effective delivery method to overcome challenges of the current oral, intraventricular, intrathecal, and intravenous methods that have added complications of side effects and/or difficulty in achieving minimum inhibitory concentration at the site of the infection, as well as avoiding the selective blood-brain barrier. Advances in understanding the mechanisms of drugs penetration of the central nervous system offer unprecedented opportunities for the development of novel therapeutics interventions. Future research is needed to identify and/or formulate drugs that can cross the biological barriers effectively without affecting the host cell viability, and test chemotherapeutic approaches such as intranasal application of drugs that can deliver drugs effectively to the site of infection.

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Notes

The authors declare no competing financial interest.

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